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Asthmatic responses to passive cigarette smoke: Persistence of reactivity and effect of medications

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The present study assessed the persistence of cigarette-smoke reactivity and the effects of drug pretreatment on bronchial responsiveness to environmental tobacco smoke (ETS). Two groups of subjects were chosen for the study. Group I consisted of 15 atopic smoke-sensitive subjects with asthma, six of whom were defined "reactors" and nine "nonreactors" to ETS challenge. Group II consisted of 15 atopic subjects without asthma and with documented upper respiratory tract symptoms on exposure to ETS. All subjects were challenged for 2 to 6 hours with mechanically generated ETS in a static inhalation chamber. Five/six subjects in group I, who were previously demonstrated as reactors 24 months earlier, remained reactive within 1 to 2 hours of continuous ETS exposure. Pretreatment with albuterol, cromolyn, and a combination of albuterol and cromolyn 30 minutes before ETS exposure significantly diminished airway reactivity to ETS. All nine previous nonreactors in group I remained nonreactive despite rechallenge with ETS for up to 6 hours. Group II subjects challenged under identical conditions did not reveal a significant decline in FEV_1 on challenge with ETS. These studies demonstrate the persistence of ETS reactivity during a 2-year period. Although cromolyn sodium and/or albuterol can protect against reactivity, mechanisms of ETS-induced airway reactivity remain unknown. (J ALLERGY CLIN IMMUNOL 1991;88:861-9.)

Key words: *Asthma, tobacco smoke, bronchial reactivity*

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Previous inhalation-challenge studies have assessed the response of subjects with asthma to passive cigarette-smoke exposure.[1-4] Shephard et al.[1] and, subsequently, Wiedemann et al.,[2] did not demonstrate significant declines in pulmonary function or increase in airway reactivity in subjects with asthma exposed to ETS. In contrast, Dahms et al.[3] and Stankus et al.[4] reported significant (≥20%) declines in FEV_1 in atopic subjects with asthma challenged with ETS. Differences in study populations and study designs can explain these discrepant results. For example, Shephard et al. and Wiedemann et al. used relatively small numbers of subjects with asthma, of which only a fraction complained of wheezing with passive exposure to cigarette smoke and used only a single 1- or 2-hour exposure to tobacco smoke. None of these studies monitored the subjects for late-phase responses. At least in one study,[4] most subjects were atopic, and most of the subjects reacting to cigarette smoke had more severe asthma.

We have demonstrated that 33% of a population of subjects with asthma who developed symptoms (chest tightness, dyspnea, cough, and wheezing) with exposure to high concentrations of ETS experienced a >20% decline of FEV_1 after cigarette-smoke chal-

Abbreviations used

ETS:	Environmental tobacco smoke
ETSC:	ETS challenge
SSA:	Smoke-sensitive subjects with asthma
SSNA:	Smoke-sensitive subjects without asthma
TSP:	Total suspended particulate
PD_{20}:	Provocative dose of methacholine causing a 20% decline in FEV_1
BHR:	Bronchial hyperreactivity

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lenge.[4] The present study was designed to investigate the persistence of airway responsiveness to ETS by additional challenge of documented ETS reactors and nonreactors. Additionally, the occurrence of late-phase airway reactivity was assessed in both reactor and nonreactor groups. A group of atopic subjects without asthma and with upper respiratory tract complaints (nasal obstruction, rhinorrhea, and sneezing) on exposure to ETS served as control subjects. The effect of pretreatment with albuterol and/or sodium cromolyn on reactivity to ETS was also investigated in smoke-reactive subjects.

MATERIAL AND METHODS

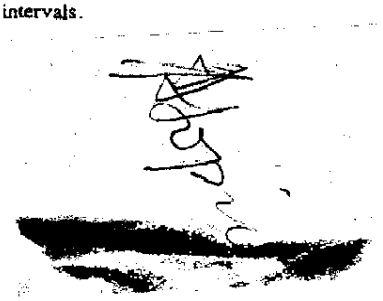
Subjects

The study participants were recruited from a large group of subjects with asthma who had been participants in cigarette smoke–challenge studies 24 months previously. Group I: SSA consisted of 15 adult, smoke-sensitive, atopic subjects with asthma who claimed symptoms of asthma on exposure to ETS. Study subjects ranged in age from 25 to 51 years and included 12 female and three male subjects. All subjects with asthma were "smoke sensitive"; that is, they claimed symptoms of chest tightness, shortness of breath, and/or wheezing on exposure to ETS. Fourteen of the 15 subjects with asthma exhibited a positive methacholine-challenge test. Group II: SSNA consisted of 15 atopic volunteers without asthma. The study subjects without asthma who also had been participants in cigarette smoke–challenge studies previously, ranged in age from 21 to 48 years and included 10 female and five male subjects. All 15 subjects without asthma claimed upper respiratory tract symptoms (rhinorrhea, nasal obstruction, or sneeze) on exposure to ETS. Atopy was defined as consisting of symptoms of rhinitis and/or asthma plus immediate wheal-and-flare skin test reactivity to two or more common inhalant allergens from a skin test panel of 20 common seasonal environmental allergens.

Study design

The study design is outlined in Fig. 1. All subjects answered a questionnaire about their symptoms, past medical history, current medications, smoking history, and whether they were exposed to passive ETS at home or work. Subjects underwent methacholine challenge and skin testing before challenge with ETS. The SSA (group I) had a 2- to 6-hour challenge with 800 cpm of ETS. All reactors (≥20% fall from baseline FEV_1) to ETS were subjected to a sham challenge for 6 hours in the test chamber in the absence of ETS exposure. All nine SSA nonreactors (<10% fall from baseline FEV_1) were subjected to a 6-hour challenge with 800 cpm of ETS 4 weeks after the first challenge. All SSNA also underwent 6-hour ETSCs with 800 cpm of ETS.

The effect of albuterol, cromolyn sodium, and a combination of both on ETS-induced airway reactivity was tested by premedicating the subjects with these medications 30 minutes before challenge on 3 different days at 4-week intervals.



For premedication studies, all reactors to ETS challenge were pretreated with nebulized albuterol (2.5 mg), cromolyn sodium (20 mg), and a combination of albuterol (2.5 mg) and cromolyn sodium (20 mg) 30 minutes before the challenge with Pulmo-Aide (Devilbiss, Somerset, Pa.) nebulizer on 3 different days. The subjects were premedicated and rechallenged on 3 different days, at 4-week intervals, with ETS to examine the effect of these agents on cigarette smoke–induced bronchospasm.

Methods

Methacholine-challenge test. The methacholine-challenge test was conducted as previously described.[4] The PD_{20} methacholine was determined by linear interpolation of the last two points on the dose-response curve.[3] The PD_{20} was calculated in cumulative breath units. One cumulative breath unit equals one breath of 1 mg/ml of methacholine.

Cigarette smoke–inhalation challenge. Inhalation challenge with cigarette smoke was performed as previously described.[4] Before challenge, study subjects were instructed to avoid medications according to established guidelines.[3] All subjects underwent cigarette-smoke challenge while their asthma was stable. There were no hospitalizations, asthma exacerbations, or significant adjustments of asthma medications within the 3 months preceding the study. Briefly, after obtaining informed consent, subjects entered a static inhalation chamber (12 by 7 by 11 feet) in which a temperature of 21° C and a relative humidity of 50% to 60% were maintained. 1R4F cigarettes (Tobacco and Health Research Institute, University of Kentucky) were "smoked" with a Borgwaldt fully automatic smoking machine (Heinrich Borgwaldt, Hamburg, Germany). A total of 10 to 12 cigarettes were smoked in 2 hours to maintain the desired exposure. Both mainstream and sidestream smoke were produced. Subjects were exposed for 2 hours to the cigarette smoke at a target level of approximately 800 cpm as indicated by a Sibata (MDA Scientific, Inc., Lincolnshire, Ill.) model P5H2 light-scattering aerosol monitor. The target level of 800 cpm was achieved initially by smoking four cigarettes and subsequently lighting additional cigarettes as needed to maintain this level. Ten to 12 cigarettes were smoked during the 2-hour challenge period.

Sham challenge of reactors with asthma to ETS. All subjects defined as reactors were subjected to sham challenge on a separate day in the static chamber. Sham challenges were performed under identical conditions and for the duration of the ETSC except that no cigarettes were lit during the subjects' stay in the test chamber.

Quantitation of cigarette-smoke exposure. The level of cigarette-smoke exposure during bronchoprovocation studies was characterized by measuring airborne nicotine and TSP levels in the inhalation chamber during challenge as previously published.[4] Relative particulate levels were continuously monitored with Sibata model P5H2 light-scattering aerosol indicator and expressed as counts per minute. In addition, integrated samples for TSP were collected on preweighed 37 mm Teflon FA filters (Millipore Corp., Bedford, Mass.) for gravimetric quantitation of particulate concentration. Quantitation of airborne nicotine levels was

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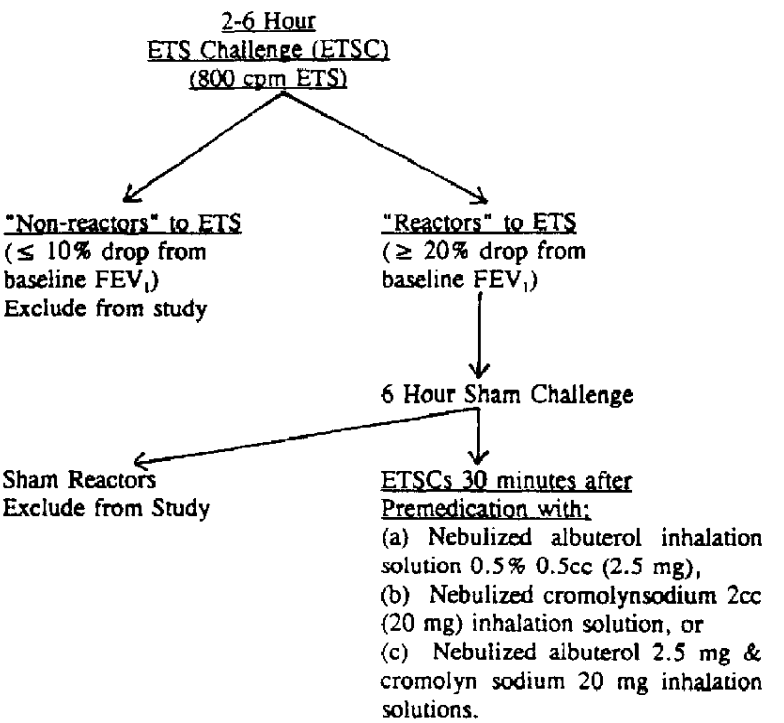

FIG. 1. Study Design. All subjects participated in ETSCs 24 months before the present studies and included both smoke-sensitive subjects with asthma (group I) and smoke-sensitive subjects without asthma (group II). Each participant completed a questionnaire, underwent physical examination, skin testing, baseline spirometry and peak flow rate determination, and a methacholine challenge. ETSCs for each subject were done at 4-week intervals to avoid any residual effect of BHR from one challenge influencing the response to a subsequent challenge.

based on modification of the method of the National Institute for Occupational Safety and Health[8] with high-performance liquid chromatography. Nicotine was collected on XAD-4 resin tubes (SKC, Inc., Eighty-four, Pa.) at a sample flow rate of 1 L/pm. Collected nicotine was desorbed with 1 ml of high-performance liquid chromatography mobile phase, and the sample was filtered and analyzed on a 30 cm Microporasil column (Waters Associates, Bedford, Mass.). The mobile phase consisted of 85:15:0.1, hexane: n-propanol: triethylamine, pumped at a flow rate of 1.75 ml/min. Nicotine was detected and quantitated by ultraviolet absorbence at wavelength of 265 nm.

Pulmonary function test. Baseline pulmonary function testing by FEV_1, FVC, and peak flow rate were performed with a Pulmonaire spirometer (Jones Medical Instrument Co., Oakbrook, Ill.). Triplicate measurements of FEV_1 were obtained at 30-minute intervals during cigarette-smoke challenge. Data are expressed as single best effort of the three determinations for each time interval. Those subjects who experienced a significant (≥20%) fall in FEV_1 were removed from the inhalation chamber and administered nebulized albuterol and/or subcutaneous epinephrine followed by repeat pulmonary function testing. All subjects were allowed to exit the chamber and terminate the challenge if at any time the exposure conditions became intolerable. Only reactors to ETS requested termination of the challenge.

Subjects who experienced a <20% reduction in baseline FEV_1 after the 2-hour challenge with ETS were rechallenged on a separate day for a period of 6 hours under identical conditions. After the ETSC, all subjects were observed for 24 hours from the commencement of the challenge, with hourly peak flow recordings in the laboratory for 10 hours, followed by another 14 hours in their homes with a mini-Wright peak flow meter (Clement Clarke International Ltd., London, England) in an attempt to identify classic late-phase asthmatic responses. Spirometry was performed at baseline and at 10 and 24 hours from the beginning of the ETS exposure.

Analysis of results. Wilcoxon's signed-rank test was used to compare the median change in protection to the airways between days with and without drug pretreatment.

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TABLE I. Demographic characteristics and methacholine challenge response of smoke-sensitive subjects with asthma and atopic control subjects

Subject No.	Age/sex (yr)	Meds*	PD_{20}† methacholine
Group I (SSA)			
Reactors‡			
1	41/M	T,B,A,S	0.3
2	38/F	T,B	0.3
3	36/M	T,B,I	1.8
4	36/F	T,B,C	2.0
5	44/F	T,B,S	3.8
6	36/F	B	NR§
Nonreactors‖			
1	25/F	T,B,S	0.3
2	27/F	B	0.8
3	40/F	T,B,A	1.2
4	41/M	B,C,A	1.3
5	41/F	B	2.3
6	51/F	T,B,S	2.5
7	35/F	B	5.0
8	26/F	B,A	5.0
9	28/F	T,B,S,I	50
Group II (SSNA)			
Nonreactors			
1	24/F	—	30
2	27/F	—	60
3	28/F	—	160.0
4	31/F	—	200.0
5	25/F	—	200.0
6	21/F	A	320.0
7	37/M	—	320.0
8	42/M	—	320.0
9	27/F	A	NR
10	32/M	—	NR
11	31/M	—	NR
12	48/F	A	NR
13	44/F	—	NR
14	22/F	—	NR
15	30/M	—	NR

*Meds, Medications: *T*, theophylline; *B*, bronchodilator (sympathomimetic); *S*, steroid (oral); *A*, antihistamines; *I*, inhaled steroid; *C*, cromolyn sodium.

†PD_{20} Methacholine in cumulative breath units.

‡Reactors experienced a >20% decline from baseline FEV_1 on ETS challenge.

§*NR*, nonreactive, a <20% decline from baseline FEV_1 after exposure to 640 cumulative breath units of methacholine.

‖Nonreactors demonstrated a <10% decline from baseline FEV_1 on ETS challenge.

RESULTS

Study population

Demographic characteristics, medications, and response to methacholine challenge of the study subjects are presented in Table I. Of the 15 SSA, seven subjects never smoked cigarettes and eight were exsmokers for more than 5 years. Thirteen of the SSA were atopic and two were nonatopic. Although all reactors to ETS except one subject were highly sensitive to methacholine, there was no definite correlation between degree of methacholine sensitivity and reaction on ETSC because most nonreactors to ETS were also very sensitive to methacholine. Of the SSNA, 12 never smoked cigarettes and three were nonsmokers for more than 5 years. All SSNA were atopic.

ETSC of smoke-sensitive subjects with asthma (group I)

Study subjects were challenged with 800 cpm of ETS that corresponded to TSP level of 1145 ± 325 $\mu g/m^3$ and airborne nicotine level of 205 ± 54 $\mu g/m^3$. Of the 15 SSA subjects, nine were classified

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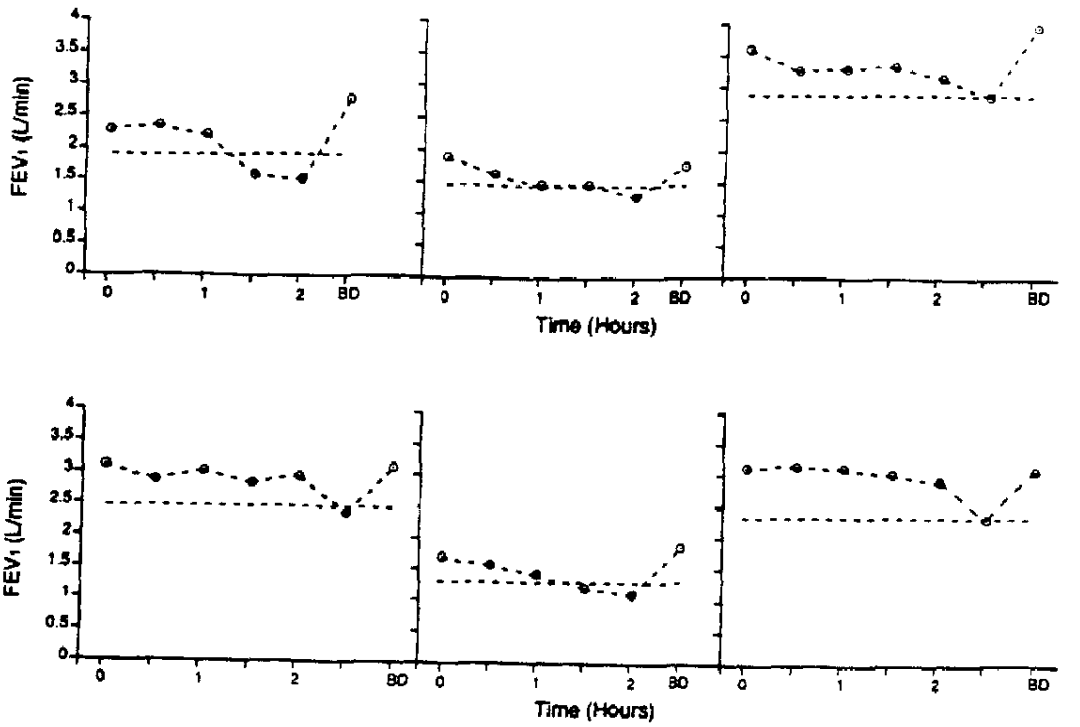

FIG. 2. Responses of six SSA reactors to ETS performed 24 months before the present challenges. *BD*, response on bronchodilator administration; *dotted horizontal line*, time of reaction, i.e., ≥20% fall from baseline FEV_1.

as nonreactors, whereas six subjects were classified reactors based on challenge studies performed 24 months earlier (Fig. 2). Five of the six reactors again experienced a >20% decline from baseline FEV_1 on rechallenge with ETS (Fig. 3) after 1 to 2 hours exposure. When the time of reaction and the extent of drop in FEV_1 are considered, two of the six SSA (previous reactors) demonstrated increased sensitivity to ETS on rechallenge, whereas the remaining four SSA were less sensitive. None of the five reactors experienced a decline of ≥20% from baseline FEV_1 during sham challenge. All nine subjects with asthma previously characterized as nonreactors experienced a <20% decline from baseline FEV_1 on repeat smoke challenges of 2-hour and 6-hour duration on 2 separate days 4 weeks apart (Fig. 4).

Analysis of late-phase airway response after ETSC

All study subjects were observed in the laboratory with hourly peak flow recording for 10 hours after commencement of the ETSC. Subjects were additionally monitored for 14 hours at their homes with a mini-Wright peak flow meter. Neither reactors nor nonreactors to ETSC (group I and group II) demonstrated classic pulmonary late-phase or dual reactivity.

Effect of drug pretreatment on ETSC

All five reactors to ETS were pretreated with nebulized albuterol (2.5 mg), cromolyn sodium (20 mg), and a combination of albuterol (2.5 mg) and cromolyn sodium (20 mg) 30 minutes before the ETSC. All five reactors pretreated with the three different drugs were rechallenged with ETS on 3 different days. As illustrated in Fig. 5, albuterol and cromolyn sodium pretreatment protected airways from the effects of ETS for up to 360 minutes. The reactivity of one subject was not altered by albuterol. In another subject, cromolyn pretreatment was not administered. Inhaled cromolyn resulted in protection of longer duration than inhaled albuterol. Protection afforded to the airways by each drug or drug combination was compared to the effects of ETS on airways on the day without premedication. Wilcoxon's signed-rank test was used to test the median change between these days. Protection to the airways afforded by albuterol or cromolyn sodium was marginally significant ($p = 0.06$).

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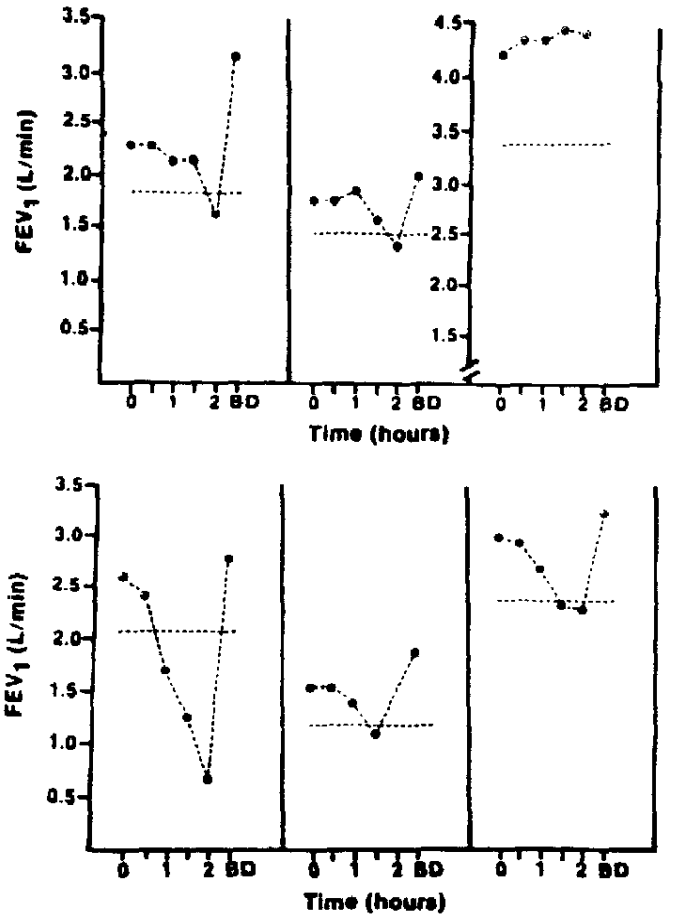

FIG. 3. Responses of six previously identified (24 months earlier, see Fig. 1) reactors to ETS. *BD*, response on bronchodilator administration. *Dotted horizontal line*, time of reaction, i.e., ≥20% fall from baseline from FEV_1.

However, the combination of both the drugs produced significant protective benefit ($p = 0.03$).

ETSC of atopic subjects without asthma (group II)

Fifteen atopic subjects without asthma with upper respiratory tract symptoms (group II) on exposure to ETS underwent a 6-hour cigarette-smoke challenge identical to the challenge of the smoke-sensitive non-reactor group with asthma. None of the 15 subjects without asthma experienced a >10% decline from baseline FEV_1 on ETSC. These findings were identical to their previous challenge results performed 2 years previously.

Extrapulmonary manifestations of cigarette-smoke exposure

Most (two thirds) of the SSA and SSNA reported severe odor intensity and nasal and eye irritation. Less than one third of the subjects reported throat irritation, and three subjects complained of headaches and nausea.

DISCUSSION

The findings of the present study confirm our previous observations of reactivity to ETS in SSA and demonstrate that this airway reactivity to ETS remains unchanged for relatively long (at least 2 years) periods

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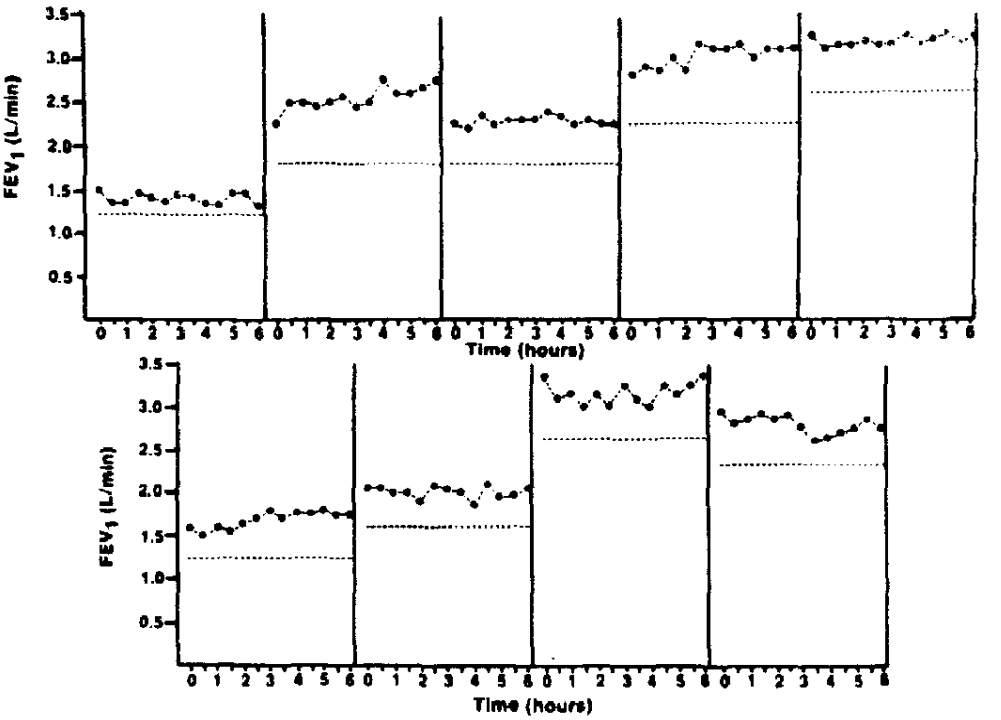

FIG. 4. Challenge responses of previously identified SSA nonreactors to ETS. *Dotted horizontal line,* 20% decline in baseline FEV_1.

of time in most smoke-sensitive subjects with asthma. Of equal importance is the fact that nine previous nonreactors remained nonreactive on reexposure to ETS during this same time period. The negative sham-challenge responses of reactors demonstrated that their airway responses to ETS could not be attributed to stopping *medications* for the study or other environmental or psychologic factors. All 15 SSNA remained nonreactive to ETS on repeated inhalation challenges.

One previous reactor was nonreactive to ETS on rechallenge with ETS, although he had previously reacted to ETS after 2½ hours of exposure. When the smoke-challenge interval was increased from 2 to 6 hours, he reacted with a >20% drop in FEV_1 (results not presented). It is interesting that this individual demonstrated an apparent change in sensitivity to ETS rather than a change in reactivity per se. This change in sensitivity could be related to treatment with inhaled steroids since the original challenge. Of the three subjects who had been taking either oral or inhaled steroids since the original challenge (24 months ago), all subjects were less sensitive (time of occurrence of the reaction and percentage of fall in FEV_1) to ETS on rechallenge. This finding could be due to the anti-inflammatory properties of the corticosteroids.

The dynamics of reactions to ETS were of interest. All reactors demonstrated a gradual decline in FEV_1 during a period of 60 to 120 minutes of continuous ETS exposure inside the static test chamber. No subject reacted to ETS before 60 minutes of smoke exposure and no classic late-phase pulmonary response at 5 to 6 hours after exposure was observed. Thus, cigarette-smoke reactivity apparently differs from the classic immediate and late asthmatic responses induced by allergen-inhalation challenge.

Immediate responses to allergen inhalation are inhibited or reversed by bronchodilators and cromolyn sodium, as was the case in our cigarette smoke–challenge studies. Cromolyn sodium afforded protection against ETS of longer duration than albuterol, but this difference was of only marginal statistical significance. Since the reactivity to ETS after 60 to 120 minutes of continuous passive cigarette-smoke exposure may be indicative of induction of airway in-

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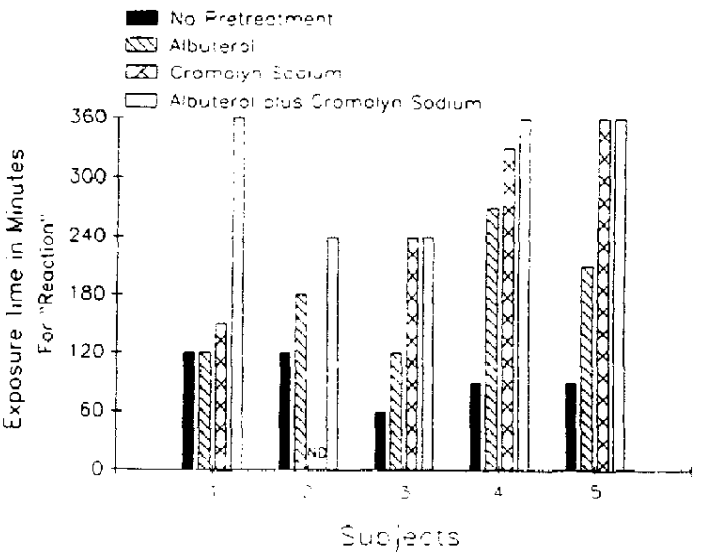

FIG. 5. Effects of premedication with albuterol, cromolyn sodium, and combination of albuterol and cromolyn sodium on SSA reactor responses to ETS. Reaction is defined as ≥20% decline from baseline FEV_1; *ND*, not done.

flammation, anti-inflammatory properties of inhaled cromolyn sodium might explain its effectiveness in blocking the irritant effects of ETS on airways.

Recent studies in our laboratory have demonstrated a significant increase in airway reactivity to methacholine after ETS challenge.[7, 8] This airway hyperreactivity was persistent for up to 5 weeks in SSA. Atopic subjects without asthma also demonstrated an increase in BHR. Of interest is the fact that this increase in BHR was observed in subjects who did not experience significant declines in FEV_1 after ETSC. It would be of interest to determine the effects of cromolyn on the increased response to methacholine observed after ETSC. Studies are underway in our laboratory to investigate this issue. Presently, however, the role, if any, of airway inflammation in the response to ETS remains undefined.

An anticholinergic agent, ipratropium bromide,[9] has been demonstrated to prevent the bronchoconstrictor effect induced by cigarette-smoke exposure in subjects with asthma, indicating that these reflexes are mediated via the vagus nerve. It is possible that neuropeptides are released during local axon reflex mechanisms and airway responses to nonspecific irritants.[10] Indeed, volatile organic chemicals, such as toluene diisocyanate have been demonstrated to increase reactivity of airways induced by neuropeptides and decreased neutral endopeptidase activity after inhalation in animal-model studies.[11] There are, however, no published studies as to the release of mast cell mediators or neuropeptides in the human airways on exposure to ETS.

The only SSA who reacted to ETS 24 months previously and had since been taking cromolyn sodium did react after 60 minutes of ETS exposure on rechallenge. This finding suggests that long-term use of cromolyn did not afford protection of the airways against the effects of ETS. However, after pretreatment with nebulized cromolyn sodium 30 minutes before ETS bronchoprovocation, this subject did not react to ETS, even after 240 minutes of exposure. Although it is possible that this subject was noncompliant, it is difficult to make definite conclusions based on observations made with only one subject. Perhaps local concentration of cromolyn sodium on the bronchial tree at the time of ETS exposure was crucial in its protective effect against irritants such as ETS. The protective effect of cromolyn might have been due to its ability to block mast cell mediators,[12, 13] inhibit eosinophil recruitment,[14] or inhibit activation of inflammatory cells.[15, 16] Cromolyn sodium has also been known to inhibit excitatory responses of "C" fiber sensory nerve endings,[17] which initiate reflex bronchoconstrictor responses.[18]

No correlation between methacholine sensitivity and airway reactivity to ETS could be established. There were no significant differences in sensitivity to methacholine observed in subjects within 2 years of repeated ETSC. The fact that one SSA reactor to ETS in the original and current study was nonreactive on

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methacholine challenge was unresolved. Although pre- and post-ETS exposure methacholine challenges were not done in the present study, the effect of ETS on methacholine responses was investigated more extensively in a separate study.[7]

Attempts were made in this study to simulate exposure conditions to ETS in the challenge-chamber atmosphere to real life situations as closely as possible. The level of cigarette-smoke exposure for our inhalation challenge was carefully monitored by measuring airborne nicotine and TSP levels. Nicotine is generally considered to be the most specific marker for ETS, since there are no significant sources of it other than ETS. In one study,[2] very high carbon monoxide (40 to 50 ppm) was reported, and in another study,[1] very high TSP (2 to 4 mg/m^3) levels were observed in the challenge atmospheres. The airborne nicotine and TSP levels generated in the present study are in the upper range of concentrations reported to exist in public places.[19]

In the present study, we attempted to assess the response of the airways of SSA to short (2 hours) and long (6 hours) durations of ETS exposure. A challenge duration of less than 2 hours was selected based on our prior experience that reactivity of subjects to ETS always occured 60 minutes or later as compared to the immediate IgE-mediated reaction induced by allergen bronchoprovocation. Since a stay for more than 6 hours in a restaurant or barroom with excessive amounts of cigarette smoke is unlikely, we selected setting a 6-hour time limit to ETSC as reasonable to identify reactors to ETS.

Our present findings with a group of SSA and SSNA confirm previous observations and provide additional support for the persistence and specificity of ETS-induced bronchial reactivity for more than a 2-year period. Although the mechanism(s) of ETS-induced airway responses are as yet undefined, pretreatment with cromolyn sodium and albuterol can protect against ETS reactivity. Additional studies to define the role of airway inflammation, the changes in airway reactivity, and the mediators involved in ETS-induced bronchospasm are clearly warranted, and such studies are now in progress.

We thank Mrs. Josephine D. Stankus, Mr. Cedric Wilson, and Mr. Byron Lockhart for their expert technical assistance, and Janet Hughes, PhD, for her help with the statistical analyses.

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